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Is the EuroSCORE II best suited for Reoperative Risk Estimation in Patients with Structural Deterioration of Aortic Bioprostheses?

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Introduction

The transcatheter aortic valve implantation (TAVI) is a feasible option for patients with severe aortic valve disease and deemed to have excessive surgical risk on the basis of preoperative comorbidities. Generally, the population of patients referred for TAVI reflects a logistic EuroSCORE I >20%, a STS score >10% and an EuroSCORE II >7% for perioperative mortality [1]. The use of risk prediction systems has gained growing importance for the systematic decision for either strategy (surgery or TAVI) in the individual patients, although several other factors are taken into consideration [2]. Nonetheless, the reliability of scoring systems in the prediction of operative mortality for aortic valve replacement (AVR) has been largely questioned. The EuroSCORE I models tend to overestimate the risk of primary AVR and to be inappropriate for the definition of candidates to TAVI [3]. Such overestimation is particularly evident in the 'high risk' cases, i.e. the subgroup in which we need more frequently to make a decision among alternative strategies [4]. The EuroSCORE II is reportedly more reliable than previous versions in the prediction of mortality in primary aortic valve replacement.

In such a scenario, the feasibility of the Valve-in-Valve procedure [5, 6] in patients with structural degeneration (SVD) of aortic valve bioprosthesis imposes an even more complex decision-making process. The Valve-in-Valve technique consists in delivering a transcatheter valve within a failing bioprosthesis (Figure 1). In fact, still limited data are available over the immediate results of this approach and population-specific variables exist (i.e. different mechanisms of bioprosthetic failure, characteristics of the primary surgery). Additionally, the risk of reoperation on the aortic valve has considerably

decreased during the recent years [7, 8, 9], and this may further challenge the validity of risk assessment.

Hypothesis

We postulate that the EuroSCORE II performs better than other risk algorithms in patients undergoing reoperation for SVD of an aortic bioprosthesis. The limits of the EuroSCORE I in these individuals have been recently evidenced [8].

Evaluation of the Hypothesis

Preliminary testing of the hypothesis was based on a comparison of the performance of three risk prediction systems (logistic EuroSCORE I, STS Score and EuroSCORE II) within a population of patients reoperated for SVD in a single center. A prospective database is conducted in our Institution for all patients undergoing cardiac surgery since 1975, and includes both pre- and intraoperative characteristics, as far as the early postoperative results. In May 2012, the database was queried in order to identify the records of patients who received reoperation on the aortic valve due to a diagnosis of structural valve deterioration (SVD) of a previously implanted bioprosthesis (index reoperation). The performance of any associated procedure to AVR at the time of primary operation did not represent an exclusion criterion. Conversely, we excluded all individuals whose primary indication to redo surgery was not a dysfunction of the aortic bioprosthesis and the patients undergoing multiple-valve procedures at the time of the index reoperation. Other mechanisms of bioprosthetic dysfunction than SVD (namely nonstructural valve

dysfunction, NSVD, and infective endocarditis, IE) were excluded as they do not represent an indication to the Valve-in-Valve procedure.

We adopted the definitions accepted by the current recommendations for reporting morbidity and mortality after cardiac valve interventions [10]. In particular, SVD was defined as any dysfunction or deterioration of the bioprosthesis which is intrinsic to the valve components, such as wear, fracture, calcification, tear, and suture line disruption, and which determines clinically significant stenosis and/or regurgitation. NSVD was any abnormality not intrinsic to the bioprosthesis itself, such as entrapment by pannus, tissue or suture, paravalvular leak or inappropriate positioning, which result in clinically significant stenosis and/or regurgitation. Finally, IE was defined as any infection of the bioprosthesis as confirmed by either findings at reoperation/autopsy or by the Duke criteria. Operative mortality was defined as death within 30 days after surgery or before hospital discharge. The terms 'scoring system', 'risk prediction system' and 'risk calculation system' were interchangeably used to indicate the Logistic EuroSCORE I, the EuroSCORE II and the Society of Thoracic Surgeons (STS) score.

Full clinical records for each subject were retrieved. The clinical data contained in the full records were retrospectively used to calculate the predicted risk at the index reoperation for each enrolled patient. The logistic EuroSCORE I and the EuroSCORE II were determined using the calculator available online at www.euroscore.org. The STS score was obtained by the calculator publicly available at www.sts.org. The additive EuroSCORE I was not considered, given its known unreliability to the purposes of risk assessment in candidates to TAVI [11]. .

Statistical analysis.

Data are presented as either mean \pm standard deviation (continuous variables) or as percentages (categorical variables). The calibration of scoring systems in predicting the mortality at index reoperation was assessed through the Hosmer-Lemeshow goodness-of-fit test. For this test, a p value higher than 0.05 indicates an adequate calibration. A Receiver Operating Characteristic (ROC) curve was built for each scoring system and the area under the ROC curve (AUC) was quantified as a measure of discrimination (*c* statistic: discriminatory ability of the system). Opposed ROC curves (and the corresponding AUCs) were compared according to the Hanley and McNeil methodology. The alpha level was 0.05. The analyses were conducted using the SAS ver. 9.3 software for Windows.

Empirical Data

The study population consisted of 81 patients whose preoperative risk profile is reported in Table 1. The mean age was 65.8 years, entailing a wide age range (from 32.6 to 86.9 years). Fifty-one patients (63%) came to index reoperation while in NYHA class III or IV, while the priority was non-elective in 16% of cases. The prevalent bioprosthetic dysfunction observed at preoperative echocardiography and/or left heart catheterization

was regurgitation in 33.4% of cases and stenosis in 18.5% of cases, while a mixed steno-regurgitant lesion was observed in the majority of patients (48.1%). Concomitant coronary bypass surgery had been realized at the time of primary surgery in 6.2% of patients, while 4.9% had received concomitant surgery on any other valve than the aortic. The failing bioprosthesis was replaced with a novel biological valve in 51.9 of patients, while the remainders received a mechanical prosthesis. Associated procedures at index reoperation were surgery of the ascending aorta in 7.4% of patients and septal myectomy in 1.2%.

The operative mortality for index reoperation was 4.9% (4 patients). Death was cardiac-related in 3 out of 4 cases (postoperative myocardial failure) and non-cardiac in one case (multiorgan failure). Operative morbidity included a 2.5% rate of surgical revision for bleeding, a 6.2% rate of prolonged (>24 hrs) mechanical ventilation, and a 7.4% rate of acute renal insufficiency.

Compared with a 4.9% operative mortality rate, the average logistic EuroSCORE I was $15.8\% \pm 13.4$, the average EuroSCORE II was $7.3\% \pm 7.4$ and the average STS score for operative mortality was $15\% \pm 9.8$. Hence, all the available scoring systems overestimated the operative mortality. Concerning calibration, the results of the Hosmer-Lemeshow test indicated that all of the three scoring systems taken into analysis are adequate ($p=0.847$, $p=0.999$ and $p=0.9948$ for the logistic EuroSCORE, the EuroSCORE II and the STS Score for mortality, respectively). The calculation of AUC of the ROC curves indicated that the three scoring systems were good predictors of mortality in the entire population. Nonetheless, the EuroSCORE II yielded an excellent 0.9903 AUC, which was significantly higher than the AUC obtained from the logistic EuroSCORE I (AUC=0.8994, $p=0.044$), but not statistically different than the AUC obtained from the STS Score (AUC=0.9643, $p=0.293$ vs. the EuroSCORE II). The STS Score did not display a statistically higher AUC than the EuroSCORE I ($p=0.118$) (Figure 2). The odds ratios obtained from logistic regression for

each score were 1.079 (confidence interval: 1.021 to 1.141) for the logistic EuroSCORE I; 1.474 (confidence interval: 1.079 to 2.013) for the EuroSCORE II; 1.223 (range: 1.056 to 1.416) for the STS Score. Thus, a one unit increment in the calculated EuroSCORE II for each patient is associated with the greater increase in the actual operative mortality, compared with the other systems.

The postoperative follow-up yielded for analysis a total of 612 patient-years. The overall actuarial survival rate was $82.1\% \pm 4.7$ at 5 years, $56.3\% \pm 6.8$ at 10 years and $45.9\% \pm 7.3$ at 15 years.

Consequences of the Hypothesis

The Valve-in-Valve technique to treat SVD is becoming an increasingly standardized procedure [5], and optimal candidate selection is pivotal for the achievement of adequate results. One most problematic issue in the decision-making between TAVI and conventional operation is the expected risk associated with open surgery. In fact, TAVI is currently reserved to patients whose operative risk is considered to be excessive due to

comorbidities and other factors contraindicating surgery. At the current stage of evidence, conventional reoperation should not be denied to patients having reasonable reoperative risk. On the other hand, it is important to reliably identify those cases who are unlikely to survive surgery and who may benefit from a transcatheter procedure instead. Although the formal estimation of risk for conventional surgery is only one among several criteria, it plays a major role in these circumstances. Actually, there is growing need for formal and reproducible criteria to discriminate the indication to TAVI rather than to conventional surgery. At the same time, the inadequacy of some scoring systems has become evident in several investigations in the setting of primary aortic valve replacement. In the Mayo Clinic experience, a major overestimation of the risk of AVR was evident for both the additive and the logistic EuroSCORE [3, 4], and has prompted efforts to recalibrate the original logistic EuroSCORE algorithm by the introduction of correction factors [13].

The estimation of risk becomes even more challenging as the subject is moved to peculiar subgroups, such as the patients affected by SVD of a previously implanted bioprosthesis. TAVI is feasible for these patients under the form of the Valve-in-Valve procedure, and poses the same decision-making issues associated with reliability of quantitative scoring systems. The need for quantitative supports to prediction of reoperative risk is evident within all the published experiences on the Valve-in-Valve procedure [6, 15]. The hypothesis that EuroSCORE II could work better in this peculiar population was formulated by us after reports of its improved performance in primary AVR patients than the logistic EuroSCORE I. Additionally, the EuroSCORE II was developed on the basis of more recent patients cohorts, which better reflect the present status of surgical candidates and of perioperative care. The early mortality after Valve-in-Valve procedure in the first published registries ranges from 12% [22] to 15% [6] and 17% [23], faced to an average baseline EuroSCORE I equal to 31%, 27% and 35%, respectively, which indicates overestimation and raises questions about score calibration..

Optimal verification of such hypothesis would require large patients' cohorts and a multi-institutional collaboration. Yet, preliminary testing on a more limited, single-Institution series was also needed as uncommon risk factors and their unusual combinations are more likely to occur in SVD patients [4]. The present preliminary testing of the hypothesis suggested that all of the tested models uniformly overestimated the mortality of index reoperation: predicted 15.8% for the EuroSCORE I, 7.3% for the EuroSCORE II and 15% for the STS Score, faced to a 4.9% observed operative mortality. SVD patients seem to behave like primary AVR candidates to this respect. This finding may be at least partly due to an excessive weight attributed to the factor 'Reoperation' in the constitution of the mathematical models. In the EuroSCORE I model, the 'Previous cardiac surgery' categorical variable is associated with a β coefficient of 1.00265 in the regression equation. Only a few major risk factors (severe left ventricular dysfunction, active endocarditis and postinfarct septal rupture) display a more important β coefficient. Conversely, a trend towards decreasing operative mortality of redo cardiac surgery has been observed during the recent years, and the patients undergoing redo-AVR probably represent the lowest-risk category [16]. Secondly, our preliminary testing indicated that although all risk models showed adequate calibration, the EuroSCORE II presented the better discrimination (ROC curves), although limited by unsatisfactory calibration in the higher tertiles of risk in the overall cardiac surgical population [18]. This confirms the observations obtained in primary AVR candidates [17]. The SVD patients represent a distinctive population with different profile in terms of baseline features, early results and long-term prognosis compared to other indications to reoperative AVR (non-structural dysfunction and prosthetic endocarditis) [8]. The SVD patients who survive the reoperation show very good long-term survival: this features underline the need for optimal prediction in order to reserve TAVI to cases who pose actually a too elevated reoperative risk, since no data exist over the long-term durability of transcatheter prostheses. Therefore, this

preliminary testing supports the worth of programming a multi-institutional collaboration in order to achieve greater statistical power and definitively verify the hypothesis that the EuroSCORE II would work better in SVD cases than the logistic EuroSCORE I and possibly the STS Score. Whether the EuroSCORE II will be found to display insufficient performance, dedicated algorithms may be developed *de novo*, as additional specific factors contribute to the risk of reoperative AVR but are not included in any previous scoring system (such as previous coronary surgery and the presence of a patent left internal thoracic artery graft) [19, 20].

In conclusion, the hypothesis that the EuroSCORE II may be preferred to the logistic EuroSCORE I in the prediction of surgical risk in aortic valve reoperation for SVD deserves testing in large, multi-institutional cohorts. This represents a major element in the functioning of local Heart Teams. The place of the STS Score will need also to be defined. On the basis of recent data concerning enhanced long-term durability of bioprostheses [24, 25], we may expect a tendency towards implantation of biological prosthesis at an earlier age and an increase in the absolute number of patients presenting with SVD. In such scenario, we anticipate a growing importance of formal tools to assess the quality of care and to justify the clinical decisions even in a medical-legal environment.

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References

1. Durand E, Borz B, Godin M et al. Performance analysis of EuroSCORE II compared to the original logistic EuroSCORE and STS Scores for predicting 30-day

- mortality after transcatheter aortic valve replacement. *Am J Cardiol* 2013;111:891-897.
2. Zahn R, Gerckens U, Grube E et al. Transcatheter aortic valve implantation : first results from a multi-center real-world registry. *Eur Heart J* 2011;32:198-204.
 3. Brown M, Schaff H, Sarano M et al. Is the European System for Cardiac Operative Risk Evaluation model valid for estimating the operative risk of patients considered for percutaneous aortic valve replacement? *J Thorac Cardiovasc Surg* 2008;136:566-571.
 4. Osswald B, Gegouskov V, Badowski-Zyla D et al. Overestimation of aortic valve replacement risk by EuroSCORE: implications for percutaneous valve replacement. *Eur Heart J* 2009;30:74-80.
 5. Piazza N, Bleiziffer S, Brockmann G et al. Transcatheter aortic valve implantation for failing surgical aortic bioprosthetic valve. From concept to clinical application and evaluation (Part 1). *J Am Coll Cardiol Interv* 2011;4:721-732.
 6. Piazza N, Bleiziffer S, Brockmann G et al. Transcatheter aortic valve implantation for failing surgical aortic bioprosthetic valve. From concept to clinical application and evaluation (Part 2). *J Am Coll Cardiol Interv* 2011;4:733-742.
 7. Langanay T, Verhoye JP, Ocampo G et al. Current hospital mortality of aortic valve replacement in octogenarians. *J Heart Valve Dis* 2006;15:630-637.
 8. Ruggieri VG, Lenglet N, Anselmi A et al. Logistic EuroSCORE I risk analysis in aortic valve reoperations after bioprosthetic replacement. *J Heart Valve Dis* 2013 in press.
 9. Jamieson W, Burr LH, Miyagashima RT et al. Reoperation for bioprosthetic aortic structural failure – risk assessment. *Eur J Cardio-thorac Surg* 2003;24:873-878.

10. Akins CW, Craig Miller D, Turina M et al. Guidelines for reporting morbidity and mortality after cardiac valve interventions. *J Thorac Cardiovasc Surg* 2008;135:732-738.
11. Zingone B, Pappalardo A, Dreass L. Logistic versus additive EuroSCORE. A comparative assessment of the two models in an independent population sample. *Eur J Cardio-thorac Surg* 2004;26:1134-1140.
12. Bonow RO, Carabello BA, Chatterjee K et al. ACC/AHA 2006 guidelines for the management of patients with valvular heart disease. *Circulation* 2006;114:e84-e231.
13. Ranucci M, Castelvechio S, Menicanti LA, Scolletta S, Biagioli B, Giomarelli P. An adusted EuroSCORE model for high-risk cardiac patients. *Eur J Cardio-Thorac Surg* 2009;36:791-797.
14. Roques F, Nashef SA, Michel P et al. Risk factors and outcome in European cardiac surgery: analysis of the EuroSCORE multinational database of 19030 patients. *Eur J Cardio-Thorac Surg* 1999;15:816-822.
15. Wilbring M, Sill B, Tuqtekin SM et al. Transcatheter valve-in-valve implantation for deteriorated aortic bioprosthesis: initial clinical results and follow-up in a series of high-risk patients. *Ann Thorac Surg* 2012;93:734-741.
16. Luciani N, Nasso G, Anselmi A et al. Repeat valvular operations: bench optimization of conventional surgery. *Ann Thorac Surg* 2006;81:1279-1283.
17. Nashef SA, Roques F, Sharples LD et al. EuroSCORE II. *Eur J Cardio-Thorac Surg* 2012 ;41 :734-744.
18. Barili F, Pacini D, Capo A et al. Does EuroSCORE II perform better than its original versions? A multicentre validation study. *Eur Heart J* 2013;34:22-29.

19. Park C, Suri R, Burkhart H et al. What is the optimal myocardial preservation strategy at re-operation for aortic valve replacement in the presence of a patent internal thoracic artery? *Eur J Cardio-Thorac Surg* 2011;39:861-865.
20. He G, Acuff T, Ryan W, He Y, Mack MJ. Determinants of operative mortality in reoperative coronary artery bypass grafting. *J Thorac Cardiovasc Surg* 1995;110:971-978.
21. Butany J, Nair V, Leong SW, Soor GS, Feindel C. Carpentier-Edwards Perimount valves – morphological findings in surgical explants. *J Card Surg* 2007;22:7-12.
22. Bedogni F, Laudisa ML, Pizzocri S et al. Transcatheter valve-in-valve implantation using CoreValve Revalving System for failed surgical aortic bioprostheses. *JACC Cardiovasc Interv* 2011;4:1228-1234.
23. Eggebrecht H, Schafer U, Treede H et al. Valve-in-Valve transcatheter aortic valve implantation for degenerated bioprosthetic heart valves. *JACC Cardiovasc Interv* 2011;11:1218-1227.
24. Ruggieri VG, Flécher E, Anselmi A et al. Long-term results of the Carpentier-Edwards supraannular aortic valve prosthesis. *Ann Thorac Surg* 2012;94:1191-1197.
25. Grunkemeier GL, Furnary AP, Wu Y, Wang L, Starr A. Durability of pericardial versus porcine bioprosthetic heart valves. *J Thorac Cardiovasc Surg* 2012;144:1381-1386.

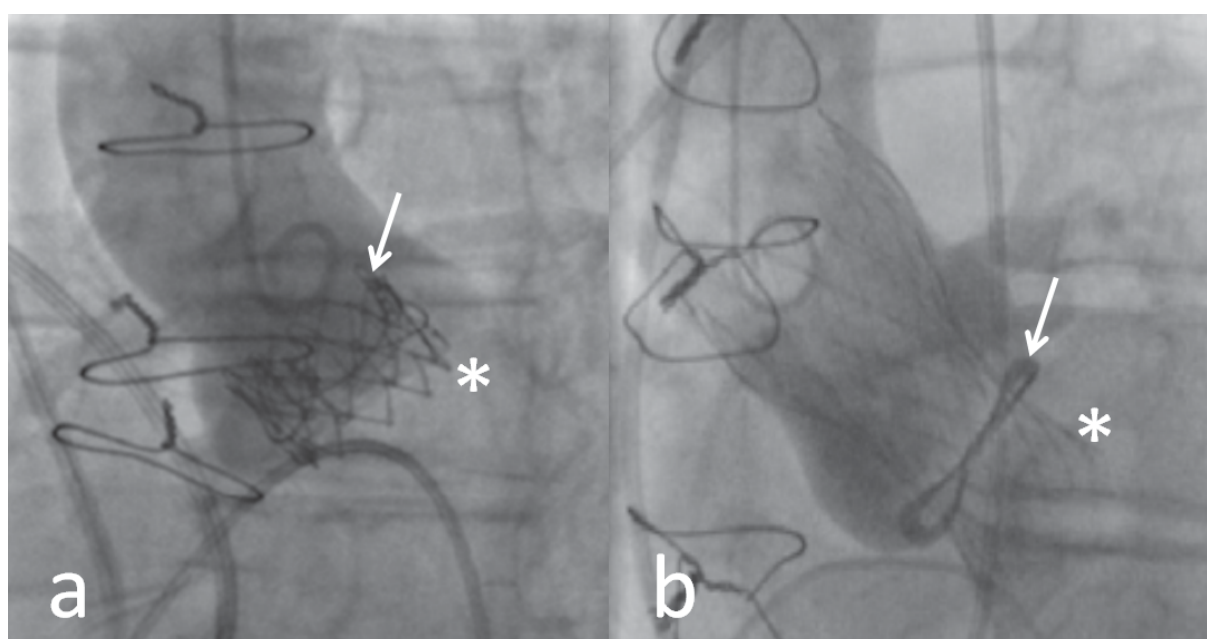
Table 1. Preoperative risk profile in the study population. *Based on the findings of preoperative echocardiography and left heart catheterization.

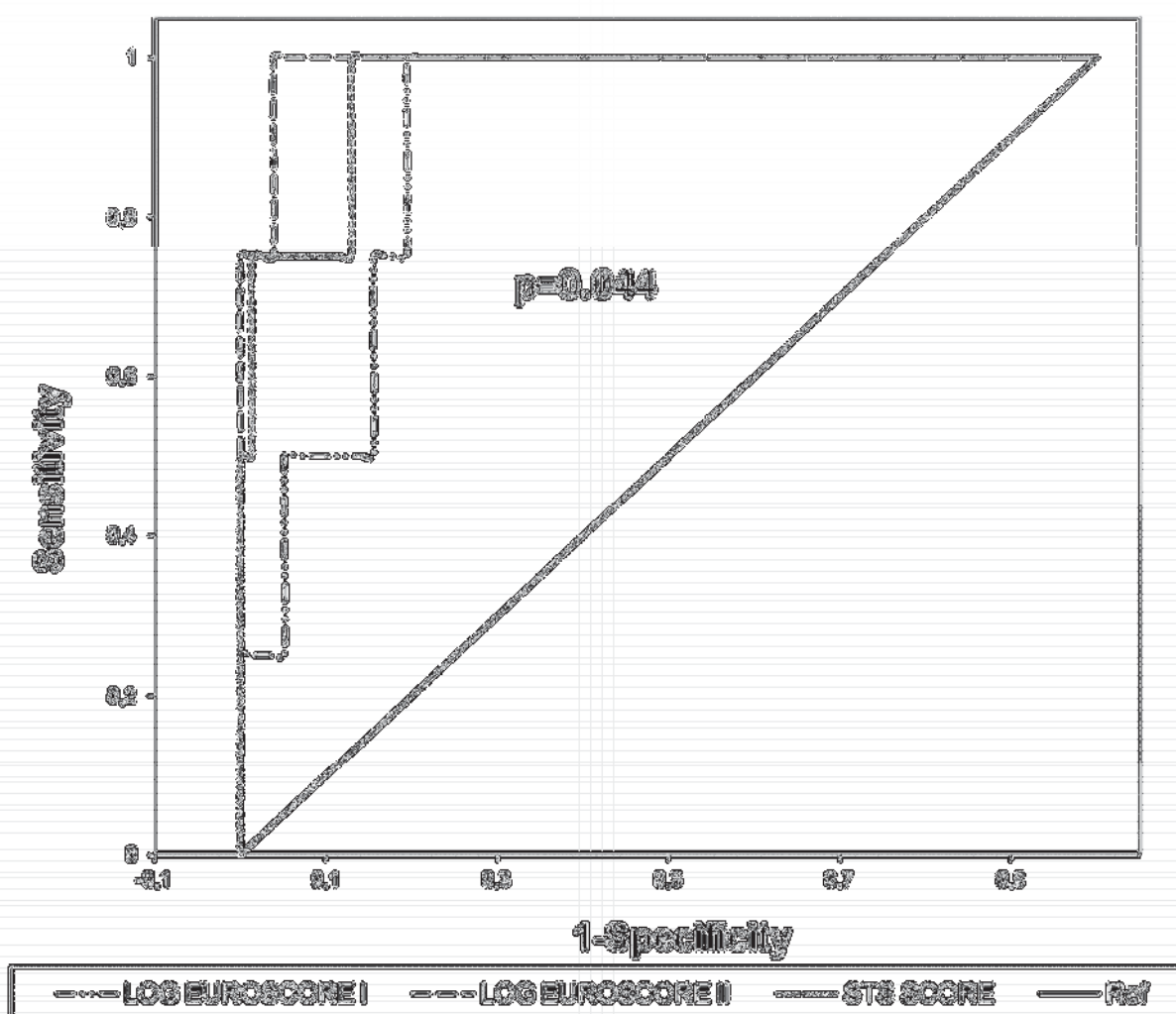
Characteristic	
Male/Female	79% / 21%
Age (years)	65.8 ± 14.9
NYHA class III or IV	51 (63%)
Previous stroke/TIA	3 (3.7%)
Diabetes mellitus	3 (3.7%)
Obesity	7 (8.6%)
Renal insufficiency	5 (6.2%)
Extracardiac arteriopathy	3 (3.7%)
Chronic lung disease	7 (8.6%)
Pulmonary hypertension	6 (7.4%)
Left ventricular ejection fraction (%)	55.1 ± 11.6
Concomitant procedure at primary surgery	
- Mitral valve replacement	1 (1.2%)
- Mitral valve repair	2 (2.5%)
- Tricuspid valve repair	1 (1.2%)
- Coronary bypass	5 (6.2%)
Non-elective surgery (index reoperation)	12 (14.8%)

Figure Legends

Figure 1. Fluoroscopic images of Valve-in-Valve implantation. Two models of transcatheter valves (a: Sapien transcatheter valve, Edwards Lifesciences Inc., Irvine, CA; b: CoreValve Revalving System, Medtronic Inc., Minneapolis, MI) (white asterisks) are delivered within two failed aortic bioprostheses (white arrows).

Figure 2. Receiver Operating Characteristic (ROC) curves for the three risk prediction systems taken into analysis. The AUC value is 0.9903 for the EuroSCORE II, 0.9643 for the STS Score and 0.8994 for the logistic EuroSCORE I. The reported p-value is for the comparison between the EuroSCORE II and the logistic EuroSCORE I.





Abstract

Background. Operative risk prediction systems (logistic EuroSCORE I, EuroSCORE II and STS Score) are employed together with multidisciplinary discussion to contraindicate conventional surgery in patients with valvular heart disease and propose the employment of alternative transcatheter procedures. The EuroSCORE I has been reported to underperform in these circumstances; we hypothesize that the EuroSCORE II is best suited for the stratification of risk in patients with structural deterioration of valvular bioprostheses and potential candidates to the Valve-in-Valve procedure (deployment of a transcatheter valve within a failing valvular bioprosthesis).

Methods and evaluation of the hypothesis. A multi-Institutional collaboration is required to fully address such hypothesis. Therefore, we performed a preliminary validation study by retrieval of the complete records of 81 patients undergoing reoperative aortic valve replacement for preoperative diagnosis of bioprosthetic SVD at our Institution. Logistic EuroSCORE I, EuroSCORE II and STS Score were calculated by preoperatively available data. Faced to an observed reoperative mortality of 4.9%, average EuroSCORE I was $15.8\% \pm 13.4$, EuroSCORE II was $7.3\% \pm 7.4$ and the STS Score was $15\% \pm 9.8$. The three systems provided sufficient adequacy (Hosmer-Lemeshow $p=0.847$, $p=0.999$ and $p=0.9948$, respectively). Yet, the area under the ROC curve was significantly higher for the EuroSCORE II (0.9903) vs. the EuroSCORE I (0.8994) ($p=0.044$). The STS Score yielded an intermediate figure (0.9643). The odds ratios (logistic regression) were 1.079 for EuroSCORE I, 1.223 for the STS Score and 1.474 for EuroSCORE II.

Conclusions. The three investigated algorithms showed reasonable calibration in the prediction of mortality for reoperative aortic valve replacement, but they evenly overestimated the observed mortality. The hypothesis that the EuroSCORE II is better suited for the selection of candidates to Valve-in-Valve implantation is worth of further

multi-Institutional investigations on the basis of our preliminary findings and due to the expanding role of transcatheter techniques.

To the attention of:

Mehar Manku, MD

Editor-in-chief, Medical Hypotheses

I undersigned Dr Amedeo Anselmi, on behalf of all co-authors of the manuscript entitled "*Is the EuroSCORE II best suited for Reoperative Risk Estimation in Patients with Structural Deterioration of Aortic Bioprostheses?*", submitted for consideration in *Medical Hypotheses*, herewith declare that there is no commercial association which may pose a conflict of interest in connection with the presented material, that all authors have read and approved the manuscript, and that there has been no duplicate publication elsewhere. In case of acceptance, we shall transfer the copyright to the Publisher.

Rennes, March 7th, 2014

Amedeo Anselmi, MD